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EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

Gastrointestinal Stromal Tumors Located in Stomach. Our Experience in a Group of 28 Patients

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Received: September 07, 2017; **Published:** October 11, 2017

Abstract

Background: Gastrointestinal stromal tumors (GIST) is the most common mesenchymal tumor of the gastrointestinal tract, with the most frequent site being the stomach. The present study described a group of 28 patients undergoing pathological diagnosis of GIST located in stomach.

Methods: Retrospective and descriptive study of 28 patients who underwent surgical removal of GIST located in stomach between September 2006 and June 2014. Seventeen of them were males. The middle age was 63 years (25 - 83). Twenty seven patients underwent surgery and only one of them underwent endoscopic resection.

Results: The most common form of presentation was as an incidental finding (11 patients). The most frequent location was lesser curvature (8 patients). 11 total gastrectomy, 6 subtotal gastrectomy 10 partial gastric resections and 1 endoscopic resection were performed. The postoperative lengths of stay were 12 days. They were classified according to Miettinen and Lasota´s classification at high risk (8 patients), intermediate risk (7 patients) and low risk (13 patients). Mean time of follow up was 59 months. There was no death. Three patients died on follow-up between 38 and 87 months. The 5-year survival was 33% (3 patients) in the high risk group and 100% for low and intermediate risk groups (9 patients).

Conclusions: GISTs are uncommon tumors that are more frequently in males. Surgery with negative microscopic margins is the treatment of choice. Tyrosine kinase inhibitors are used as adjuvant treatment and advance disease.

Keywords: *Gastrointestinal Stromal Tumours; GIST; Immunohistochemistry; Stomach; Laparoscopic Surgery*

Introduction

Gastrointestinal stromal tumors (GIST) are the most frequent mesenchymal tumors of the digestive tract [1]. They account for 2% of all malignant neoplasms of the gastrointestinal tract. They can be located anywhere in the abdominal cavity, being more frequent in the stomach (50 - 60%), small intestine (20 - 30%), colon (10%), esophagus (5%) and extragastrointestinal (5%) as epiplon, Mesentery or retroperitoneum [2,3]. Its incidence is 1/100,000 inhabitants per year, and are more frequent among men aged 60 - 65 years [4]. Its cells have similar characteristics to the interstitial cells of Cajal that play a regulating role in intestinal motility [5]. The immunophenotype of these cells is positive for CD117 (c-KIT) in 95%, for CD34 of 60 - 70%, actin and myosin (15 - 60%) or for S-100 (10%), being less frequent the expression of desmin, chromogranin or neurofilaments. Between 5 - 20% of GISTs are negative for CD117.

Since 1940, they were considered smooth muscle neoplasms (leiomyomas, sarcomas, etc.). In 1983 Mazur and Clark genetically designated these lesions as stromal tumors [6]. Its identification as a tumor entity was described in 1998 by Kitamura and Hirota based on the analogy with mast cells [7]. Kinblom proposed the theory that these cells came from stem cells that differed from Cajal cells [8].

The objective of our study is to present a wide series of surgically operated gastric localization GIST to analyze the presentation, diagnosis, treatment and prognosis of these tumors.

Material and Methods

Retrospective and descriptive study performed on patients operated by the General Surgery Service of our center of gastric neoplasia with final histological GIST result.

Between September 2006 and June 2014, 188 patients were treated for gastric cancer, of which, in 28 cases, the final diagnosis was GIST (17 males and 11 females) with a mean age of 63 years (range 25- 83). In all patients, GIST was diagnosed by immunohistochemical study with positivity for CD 117 (25 patients) and CD34 (19 patients) cell markers.

We analyzed aspects such as: presentation, clinical, diagnostic methods, tumor location, surgery performed, hospital stay, morbidity, mortality, tumor prognostic factors (size and number of mitoses), follow up, need for neoadjuvancy and tumor recurrence.

Data were collected and tabulated in a computerized database (Microsoft Office Excell 2016®). For the qualitative variables, the distribution of phenomena was studied, while for the quantitative variables the range and the mean were studied.

Results

Twenty-seven patients underwent surgery. In only one case was an endoscopic resection performed in the operating room through gastroscopy. The location was as follows: esophagogastric junction (3 patients), fundus (6 patients), minor curvature (8 patients), major curvature (2 patients), antrum (2 patients) and gastric body (3 patients).

The predominant clinic was upper gastrointestinal bleeding (7 patients), chronic anemia (4 patients), abdominal pain (5 patients) and dyspepsia (1 patient). In 11 patients, this was an incidental finding that was asymptomatic.

There were 11 total gastrectomies, 6 subtotal gastrectomies and in 10 cases an atypical gastrectomy (segmental resection). No laparoscopic approach was used in any intervention. Only 2 patients were operated on in the emergency room and in both cases an incidental finding).

The average stay was 12 days. No patient had metastases at the time of surgery. After the histopathological study of the resected part no microscopic involvement of the resection margins was observed. No lymph node involvement was reported in any patient. All patients underwent immunohistochemistry by the Pathological Anatomy Service of our center, using CD117, CD34, smooth muscle actin, desmin, and S-100 protein as markers (Table 1).

Patient	Size (cm)	Mitosis	Miettinen- Lasota	CD 117	CD 34	S-100	Actin	Desmin
Patient 1	12x10	< 5 / 50 HPF	High	+	+	-	-	-
Patient 2	2	< 1 /50 HPF	Low	-	-	+	+	+
Patient 3	8x7	3 / 50 HPF	Intermediate	+	-	-	-	-
Patient 4	7	20 / 50 HPF	High	+	-	-	-	-
Patient 5	2,5	<5/ 50 HPF	Low	+	+	-	-	-
Patient 6	5x4	< 2 / 50 HPF	Low	-	-	-	-	-
Patient 7	15	8 /50 HPF	High	+	+	-	-	-
Patient 8	4x3x3	0/50 HPF	Low	+	+	-	-	-
Patient 9	3x4	0/50 HPF	Low	+	+	-	+	-
Patient 10	6	> 10/ 50 HPF	High	+	-	-	-	-
Patient 11	3	< 1 /50 HPF	Low	+	+	-	-	-
Patient 12	4	0 /50 HPF	Low	+	+	-	-	-
Patient 13	11	10/ 50 HPF	High	+	+	-	-	-
Patient 14	4	<2/50 HPF	Low	+	+	-	-	-
Patient 15	6	1 /50 HPF	Intermediate	+	-	-	-	-
Patient 16	5	<5 /50 HPF	Intermediate	+	+	-	-	-
Patient 17	5x3	>5 /50 HPF	Intermediate	+	+	-	-	-
Patient 18	3x2,5	<5/50 HPF	Low	-	-	-	-	-
Patient 19	4,7x4	< 2/50 HPF	Low	+	-	-	+	-
Patient 20	11x7,5x8	>5/50 HPF	High	+	+	-	-	-
Patient 21	6,5x4,1	<5/50 HPF	Intermediate	+	+	-	-	-
Patient 22	3X2	< 2/50 HPF	Low	+	+	-	-	-
Patient 23	16x16x17	<2 /50 HPF	High	+	+	-	-	-
Patient 24	2	<1 /50 HPF	Low	+	+	-	-	-
Patient 25	4	<3 /50 HPF	Low	+	+	-	-	-
Patient 26	10	< 5/ 50 HPF	Intermediate	+	+	-	-	-
Patient 27	10x6	< 10/ 50 HPF	High	+	+	-	-	-
Patient 28	5,5	< 5/ 50 HPF	Intermediate	+	+	-	+	-

Table 1: *Patient characteristics studied.*

They were classified into different risk groups according to the Miettinen and Lasota classification of 2006 (based on size and number of mitosis): low risk (13 patients), intermediate risk (7 patients) and high risk (8 patients) [9] (Table 2).

	Size	Mitotic index
Very low risk	< 2 cm	< 5/50 HPF
Low risk	2 - 5 cm	< 5/50 HPF
Intermediate risk	< 5 cm	6 - 10/50 HPF
	5 - 10 cm	< 5/50 HPF
High risk	> 5 cm	> 5/50 HPF
	> 10 cm	Any index
	Any size	> 10/50 HPF

Table 2: *Miettinen GIST risk table (AFIP).*

There was no operative mortality. The mean follow-up of the series was 59 months (range 17-110). Overall survival was 89%. Survival in the high risk group was 62% (3 patients out of 8 who belonged to this group died) while in the intermediate and low risk groups it was 100%.

Only 3 patients died during follow-up (at 38, 61 and 87 months) due to disease progression in the form of multiple liver metastases (2 patients) or as peritoneal implants (1 patient). No patient received neoadjuvancy with tyrosine kinase inhibitors prior to surgery. Patients received adjuvant therapy (Imatinib at doses of 400 mg/24 hours v.o.). In 1 patient, Imatinib was replaced by poor tolerance to Sunitinib (dose of 50 mg/24 hours v.o.) and in another due to disease progression. In the latter, a third line of treatment with Regorafenib at a dose of 160 mg/24 hours with poor evolution was established.

Discussion

GISTs are the most common mesenchymal tumors of the gastrointestinal tract. They are non-epithelial tumors (such as non-GIST sarcomas, lipomas, leiomyomas, inflammatory fibrous polyps or plexiform fibromixomas) which arising from the submucosa, muscularis propria or serosa [10].

They account for 2% of all malignant neoplasms of the digestive tract [3]. The most frequent symptoms of gastric GIST are abdominal pain and bleeding (in the form of anemia or digestive hemorrhage) [11]. Other symptoms such as dyspepsia, jaundice and mass effect have also been described, although most patients are asymptomatic and are usually a casual finding [12]. Although they present with symptoms such as abdominal pain and clinical bleeding, most are diagnosed as incidental findings in imaging tests (computerized axial tomography, gastroscopy, etc) (Figure 1). They are microscopically detected as submucosal lesions in gastroscopy. For its diagnosis fine needle aspiration (FNA) is only reserved for indeterminate submucosal lesions or to assess the need for previous neoadjuvancy [10].

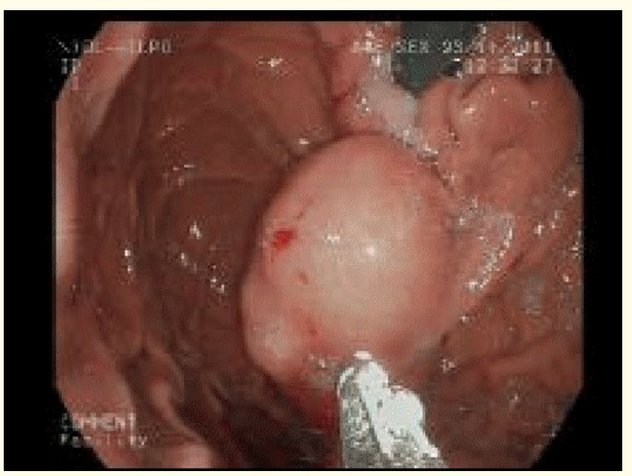

Figure 1: *Gastric GIST observed in a gastroscopy.*

Most of the GISTs are solitary lesions that are expressed in the elderly adult, with multiple or infantile age being uncommon [2]. They may be associated with other syndromes such as neurofibromatosis type I (multiple GIST or Cajal cell hyperplasia), Carney's triad (GIST, paranganglioma and chondroma pulmonary) or Carney-Stratakis syndrome (GIST and paraganglioma) [3,13].

The main treatment is surgical resection of the tumor with non-affected margins. For some authors it represents the most important prognostic factor. Lymphadenectomy associated with surgery is controversial and considered unnecessary by some authors being that the risk of recurrence and lymphatic infiltration in these patients is low. Authors such as Naguib performed lymphadenectomy in those patients with macroscopically visible lymphadenopathy and no neoplastic infiltration was documented [14]. In 2009 Agaimy and Wünsch analyzed 209 patients with GIST diagnosis, finding only 2 of them with nodal involvement [15]. Tumors located distally to the stomach and with epithelioid histology have been described as having a higher risk of lymphatic involvement. Unlike sarcomas, nodal involvement is not related to prognosis. Only lymphadenectomy seems to be indicated in those GISTs in which the molecular analysis of the tumor would have identified the mutation that implies the loss of expression of the complex B of succinate dehydrogenase present in 7.5% of the total of these tumors [3,10].

The segmental resection should be sufficient to obtain unaffected margins. In some cases, size and location may lead to more extensive surgeries as in our series (in the 11 cases located in esophagogastric junction and minor curvature forced the surgeon to perform a regulated gastrectomy instead of a segmental resection) while in the rest was due to lack of preoperative diagnosis or by size. In the series by Fujimoto., *et al*. of 140 patients with gastric GIST, 3.5% required total gastrectomy, 27.9% had a subtotal gastrectomy, and the majority, 67.8% were sufficient with atypical gastrectomy [16].

In most series the long-term results are similar to our one. The proximal gastric localization (major curvature and fundus) allows segmental gastrectomy, but for larger tumors it may interfere with gastric function or the production of gastroesophageal reflux [17] (Figure 2).

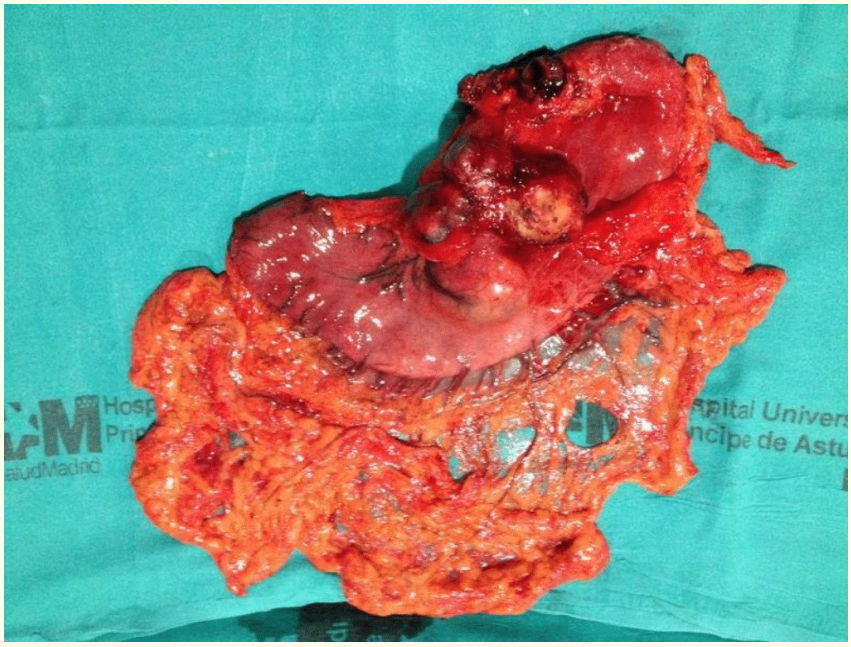

Figure 2: *Total gastrectomy by a gastric GIST located in esophagogastric junction.*

Traditionally, as good prognostic factors, size less than or equal to 2 cm, less than 5 mitosis per 50 high power field, gastric localization and not tumor rupture. For some authors the involvement of the margins in large GIST is controversial since the tumor cells are in contact with the peritoneal surface, whereas in the small ones it may be more relevant [18]. If after the resection the margin is infiltrated there is no evidence on the attitude to follow (surgical rescue, adjuvancy, observation, etc.) so it might not be an important prognostic factor.

Laparoscopic gastric resection is indicated for small tumors (less than 5 cm), avoiding excessive manipulation of the piece and by bag extraction (to reduce the risk of rupture, which is the main risk factor for the spread of these tumours) [10]. In cases of advanced disease, tyrosine kinase inhibitors have been shown to increase survival. Previously, there was no effective treatment for cases with disseminated or metastatic disease [19]. Among these, adjuvant therapy with imatinib (Glevec®) at a dose of 400 mg/24 hours v.o. is the first-line treatment for those GISTs unresectable or with disseminated disease [10]. Its interruption is accompanied by progression of the disease. However, 10 - 15% of GISTs are resistant to treatment. For these cases sunitinib (Sutent®) at doses of 50 mg/24 hours v.o. is the second line of treatment. Regorafenib is another third-line drug if could be any resistance or poor tolerance to the first two. Radiotherapy is only suggested in selected patients [20]. The recurrence of gastric GIST after surgery is 17 - 24% [11]. In our series it was 10,7%. Five patients received adjunctive therapy with imatinib at doses of 400 mg/24 hours v.o. In one patient treatment was discontinued due to poor tolerance in the form of edema, asthenia and significant anemia. In 2 cases and due to tumour progression the dose of imatinib was modified to 800 mg 24 h v.o.

Authors such as Valerie have described a 5-year survival of 96% for low-risk groups, 54% for intermediate-risk patients, and 20% for high-risk patients with a median recurrence rate of 19 - 25 months [17]. Our series presented better results in all groups with a 5-year survival of 33% for high-risk and 100% for intermediate and low-risk patients with a median survival of 38 - 87 months). In cases of locally advanced disease such as peritoneal implants and resistance to imatinib, cytoreduction surgery and intraoperative hyperthermic chemotherapy (HIPEC) seem to improve survival despite the low sensitivity of tumor cells of these tumors to doxorubicin and cisplatin [21].

In conclusion, GISTs are tumours with a low incidence and infrequent. No GIST should be considered benign. Most are asymptomatic and are diagnosed incidentally. When they are symptomatic, abdominal pain and bleeding are the most frequent symptoms. Surgical resection with non-affected margins is the treatment of choice. Radical lymphadenectomy is routinely unnecessary, since the frequency of regional lymph node metastases is very low. The laparoscopic approach of these tumours is valid for the small ones if there is no rupture or excessive manipulation. For high-grade GISTs, those with metastases at the time of diagnosis, in cases of disseminated disease or recurrences, treatment with tyrosine kinase inhibitors have shown good results in improving long-term survival.

Conflicts of Interest

The authors declare that they have no conflict of interests.

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Volume 4 Issue 1 October 2017